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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Chien, Te-Yen**	Confirmation No.: **1537**
Application No.: **10/621,711**	Group Art Unit: **1615**
Filing Date: **July 17, 2003**	Examiner: **Ghali, Isis A.D.**

For: **Transdermal Hormone Delivery System: Compositions and Methods**

DECLARATION OF AGIS KYDONIEUS PURSUANT TO 37 C.F.R. §1.132

I, Agis Kydonieus, declare as follows.

1. I am a United States citizen residing at 17 Savage Road, Kendall Park, New Jersey.

2. I received a Bachelor's degree *summa cum laude* in Chemical Engineering in 1959 and a Ph.D. in Chemical Engineering in 1964 from the University of Florida, as set forth in my professional resume attached hereto.

3. From 1960-1962, I was a chemical engineer at Union Carbide Corporation. From 1964-1968, I was a process scientist at Union Camp Corporation. I served as an Assistant Professor of Chemical Engineering at the Cooper Union Polytechnic Institute (New York, NY) from 1968-1970. During that time and until 1971 I was President and Principal of Chemtech Inc., Boston, MA. I served as Director of Research and Development at Baxter Laboratories from 1973-1974. From 1971-1973 and 1974-1988, I was employed with Health-Chem Corporation, where I served in several roles at Hercon Laboratories

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Corporation in the area of transdermal and controlled release technology, including Director of R&D, Vice President, and finally President. I was Vice President of Corporate R&D for the ConvaTec Division of Bristol-Myers Squibb Corporation from 1988-1998. Additional details of my professional history are set forth in my professional resume.

4. From 1998 to the present I have served as President of Samos Pharmaceuticals, LLC, a pharmaceutical consulting company specializing in drug delivery, including oral, transdermal, implantable, injectable, buccal and vaginal delivery. I am currently a consultant in the role of Chief Scientific Officer of Agile Therapeutics, Inc., an early stage pharmaceutical company developing transdermal hormone delivery devices.

5. I have had over forty-five years of scientific training and business experience in the chemical and pharmaceutical industry, including over thirty years in the fields of controlled release and transdermal drug delivery. I am the editor, co-editor or presenter of numerous books, book chapters, publications, invited reviews and invited lectures in these fields, as set forth in my professional resume. I hold thirty-five United States Patents, several of which are in the fields of controlled release or transdermal drug delivery. I am or have been a member of several scientific or business associations, including the Controlled Release Society, the American Institute of Chemical Engineers, the American Association of Pharmaceutical Sciences, Krikos, Inc., Society of Biomaterials, Society of Investigative Dermatology, and the New York Academy of Sciences. I am one of the founders, past president and trustee of the Controlled Release Society, the premier International Society of drug delivery. I serve, or have served, as Director of the New Jersey Center for Biomaterials & Medical Devices-Member Industrial Advisory Board, MIT Biomaterials Consortium-Member Industrial Advisory Board, Health Chem Corp, Hercon Laboratories, Controlled Release Society, Krikos, Inc, Chemtech, Inc, and Exicon Import-Export Company and on the Scientific Advisory Boards of Valera Pharmaceuticals, Inc, Kytogenics Pharmaceuticals, Inc, TyRx Pharma and Transave Pharmaceuticals.

6. As mentioned, I serve as Chief Scientific Officer of Agile Therapeutics, Inc., licensee and developer of the technology disclosed and claimed the above-referenced U.S.

Patent Application Serial No. 10/621,711, entitled "Transdermal Hormone Delivery System: Compositions and Methods" (referred to hereinafter as "the present application"), the claims of which are currently under rejection in the U.S. Patent and Trademark Office.

7. I have read and am familiar with the Official Action dated August 4, 2006 in the present application. I understand the nature of the rejections made by the examiner concerning alleged obviousness of the claimed invention over the teachings of U.S. Patent 5,876,746 ("the 746 patent") in view of U.S. Patent 5,023,084 ("the 084 patent") and, for some claims, additionally in view of U.S. Patent 5, 876,746 ("the 746 patent"). According to the examiner, it would have been obvious to provide a transdermal delivery device to deliver combined estrogen and progestin in a matrix comprising a combination of enhancers as disclosed by the 956 patent, and to add capric acid as disclosed by the 084 patent for a different type of transdermal device, motivated by the teaching of the 084 patent that capric acid provides satisfactory skin absorption enhancement in that different system; therefore a four-component enhancer combination comprising DMSO, lauryl lactate, ethyl lactate and capric acid would be expected to deliver the hormonal combination to the skin of the user at a satisfactory enhanced rate.

8. I strongly disagree that the teachings of the aforementioned patents would have rendered obvious the transdermal delivery system claimed in the present application. The three bases for my opinion in this regard are (1) that the general unpredictability of controlled release and transdermal drug delivery make it impossible to predict the outcome of changing a transdermal formulation, absent empirical experimentation and, more particularly, (2) that one seeking to improve the transdermal system of the 956 patent would not find sufficient information in the 084 patent, directed to a different type of transdermal system, to make the types of modifications that are claimed in the present application; and (3) that the significant improvement in clinical results achieved by a simple re-formulation of the skin permeation enhancer cocktail of the 956 patent, i.e., by adding capric acid , could not have been predicted from the information imparted by the cited patents. These bases for my opinion are expanded upon in the following paragraphs.

The Field of Transdermal Drug Delivery is Not Predictable

9. After over 35 years in the field of controlled release and transdermal drug delivery, it has become my view that the transdermal delivery of drugs has been easy to define and scientifically present, but it has been extremely difficult to accomplish in actual practice. Permeation of drugs through skin has been extensively studied, but the mechanism of action is not completely understood and the permeation *in vivo* difficult to predict.

10. Scientifically speaking, the permeation of a drug through skin is a function of that drug's physicochemical properties, such as molecular weight, melting point and hydrophilicity. However, the drug has to be delivered from an appropriate vehicle from which the drug can then partition into the skin. That partitioning is dependent on the relative solubility of the drug into the two environments, that of the vehicle and that of the skin. Transdermal vehicles or formulations are usually very complex because they have to perform other functions in addition to allowing maximum permeation of the drug through the skin. For example the formulations should allow adhesion to the skin for extended periods of time, prevent irritation of the skin, and be cosmetically acceptable. Therefore the formulations usually contain pressure sensitive adhesives, plastisizers, humectants, emollients, anti-irritants and other modifiers. Thus the vehicle composition greatly affects the rate and extent to which the drug permeates the dermal barrier (1, 2). Science again tells us (Fick's law of diffusion) that the permeation should be maximum when the drug is at maximum thermodynamic activity or chemical potential of unity. In an ideal system, this means that the drug should be in a saturated solution (supersaturated solutions, which would give higher permeation rates, are to be avoided because they provide unstable systems) in the vehicle. Davis and Hadgraft state that postulating the effect that a particular topical delivery vehicle will have on the permeation process is not a simple matter because the dosage form in contact with the skin is seldom a simple solution; more often it is a complex mixture of several chemicals that may interact in several (often opposing) ways as far as permeation enhancement is concerned. The "leaving potential", or thermodynamic activity of the drug in the vehicle is therefore a major factor in the delivery process (3).

11. What makes the process even more unpredictable is the fact that each of the components of the formulation has its own "leaving potential", so during the permeation process the driving forces within the transdermal formulation continuously change. Therefore, consideration of these changes as well is needed to provide a formulation with appropriate penetration rate.[1]

12. The complexity reaches even a higher level when the formulation is applied to the outside of the skin (asymmetric configuration), duplicating clinical use conditions. The reason for this additional complexity is the fact that water moves from the body or receptor phase in to the transdermal formulation thus altering the thermodynamic activity of the drug as well as all of the other components in the patch.[2]

13. The complexities mentioned above that are associated with the development and optimization of a transdermal formulation are further compounded when one considers that the drug after "leaving" the formulation will have to encounter the complexities of the biochemical environment that constitutes the dermal barrier to the ingress of chemicals. It is well understood that the lipid bilayers of the intercellular lipids within the stratum corneum with its highly oriented hydrophilic and lipophilic regions, together with the keratinized intracellular flattened corneocytes, form an excellent permeation barrier to permeation of any chemical substance (5).

14. Enhancers, and more specifically chemical enhancers, can influence permeation by increasing the solubility of the drug in the stratum corneum. This can be accomplished if

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[1] As one illustration of this, Kurihara-Bergstrom, et al., studying the effect of DMSO on the in vitro permeability of methanol, butanol and octanol (using DMSO solutions on both sides of the skin/balanced configuration) observed that the rate of octanol absorption is reduced at intermediate DMSO concentrations. They concluded that permeability may be different for hydrophilic and hydrophobic compounds, and simple measurements of net effects do not accurately reflect underlying events where competing factors are moving in opposite directions (4).

[2] As another illustrative example, Kurihara-Bergstrom, et al, studying the effect of DMSO on permeation of the alcohols mentioned above in an asymmetric configuration (DMSO solution in donor, saline solution in receptor), concluded that the rate of absorption for methanol was not affected by the application regiment and the absorption was increased 50-fold as DMSO increased to 100%. Conversely, the absorption of octanol was decreased as DMSO increased to 100%. It was postulated that competing solvent flows, DMSO moving toward the receptor phase and water moving in the donor phase introduced significant variables that accounted for this phenomenon.

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the drug has good solubility in the chemical enhancer and the chemical enhancer has good solubility in the stratum corneum lipids. In most cases however, the chemical enhancer, once it has penetrated into the dermal bioenvironment, disrupts the tight structure of the intercellular lipid bilayers thus increasing the fluidity of the lipids and increasing permeation (6,7). This disruption can take different forms such as the incorporation of medium chain length (e.g., 12 to 14 carbon atoms) fatty acids into the long chains of the stratum corneum fatty acids (8), the incorporation of kinked (e.g., oleic acid with a cis-double bond) fatty acids (9), formation of pool of enhancer liquid within the bilayer (10), or the extraction of lipids from the bilayer, thus forming a void volume through which permeation can be facilitated (4, 11).

15. It is therefore not surprising that enhancers behave substantially differently when they are co-delivered with other enhancers and vehicles to enhance the permeation of drugs. In the enhanced delivery of naloxone (8) for example, as well as other drugs (12, 13) with fatty acids, it was found that the best results were obtained when the enhancer propylene glycol was used as the vehicle, with a 150 enhancement ratio over the non-fatty acid containing control. The enhancement ratio was dropped to 10 and 2 when the co-delivered enhancers/vehicles were isopropanol and isopropyl myristate respectively.

16. In the case of DMSO, I mentioned above (4) that when it is delivered from water it did not increase the permeation of alcohols (decreased permeation of octanol) until the concentration of DMSO increased above 60%. In a companion study by the same authors, using the same experimental design, the permeation of the antiviral agent vidarabine was studied (14). Similar results were obtained as with the alcohol study, with the permeation decreasing up to 50% DMSO concentration and then rising rapidly as DMSO concentration increased to 100%. Similar results were obtained by others (15,16) when DMSO was delivered from water. In all cases, a 50 to 60 % concentration of DMSO was needed to increase the permeation of such agents as picric acid, tetrachlorosalicylanilide and radiolabelled water. In contrast, when DMSO was delivered from alcoholic solutions, a dose response was obtained for DMSO concentrations from 10% to 50% (17).

17. It is clear from the above observations that the effect of enhancers on the permeation of drugs through skin is unpredictable and dependent on many variables whose effect can only be determined by experiment. When skin permeation enhancers are used in combination, or in different solvent systems as in the case of DMSO discussed above, this unpredictability is compounded greatly.

The Modifications of the 956 Patent's System Made in the Present Application
<u>Could not be Gleaned from Information Presented in the 084 Patent</u>

18. The transdermal hormone delivery system of the 956 patent is similar to that of the present application – it was designed to deliver estrogen and progestin hormone from a single layer of adhesive polymer matrix, and utilizes a skin permeation enhancer combination containing a specified ratio of enhancers. However, the system of the 956 patent is deficient in part because it is not able to deliver sufficient amounts of progestin hormone to a woman's bloodstream to ensure contraception. The system of the present application overcomes this deficiency by making a modification to the enhancer system, namely, by adding a small amount of capric acid (about 1-12% by weight of the adhesive polymer matrix[3]). The examiner has stated that a person of skill in the art would have found all information needed to make this modification within the 084 patent. In view of the general unpredictability in the art of transdermal delivery as elaborated above, I believe this would be impossible to do.

19. It must be kept in mind that the 084 patent discloses a very different transdermal delivery system from that of the 956 patent. Instead of delivering progestin and estrogen hormones from a single adhesive polymer matrix, it utilizes a bilayer or trilayer system in which (1) the estrogen is separated into a different layer from the progestin, (2) there may be membranes between the layers, and (3) only a single enhancer is utilized, and only in the progestin-containing layer. Granted, the 084 patent presents *in vitro* skin flux data that capric acid, as a *sole* enhancer, works well in that system, but capric acid was already known generally as a good skin permeation enhancer for steroid hormones (18), so even this was not

[3] In certain exemplary embodiments, the adhesive polymer matrix is formulated with about 2.5-5% capric acid and after drying the adhesive polymer matrix contains less than about 9% by weight capric acid (about 6% in one exemplary embodiment).

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new information. Moreover, the 084 patent was not particularly instructive in suggesting what range of capric acid would be "suitable," suggesting as broad a range as 10-40% of the polymer material, 15-30% preferred. Given that the bilayer/trilayer system is quite different from the single layer adhesive polymer matrix system of the 956 patent, a skilled person would have to question what to do with this information. If capric acid works well in the bilayer/trilayer system, would it offer any improvement to the enhancer combination of the 956 patent? If so, how much capric acid should be added to the 956 patent's enhancer formulation? If 15-30% yields "highly satisfactory skin absorption enhancement and satisfactory adhesion" (084 Col. 17, lines 54-56), should 15-30% be added to the enhancer combination of the 956 patent? Should other enhancer components be reduced? If so, by how much? Should all other components be altered or only some of them? Indeed, the *in vitro* skin flux data shown in the 084 patent suggest that capric acid *alone* might function *better* than the 956 patent's combination: compare 0.49 - 1.84 $\mu g/cm^2/hr$ progestin (Tables 3 and 10) at 45-50% capric acid in the 084 patent's example patches with about 0.26 $\mu g/cm^2/hr$ progestin (calculated from Fig. 2) for 45% total enhancers in the 956 patent's example patch, using the same *in vitro* skin flux test. In view of this information, should capric acid completely replace the other enhancers of the 956 patent? In my opinion, there would be no possible way to even begin to answer these questions without significant experimentation.

20. As mentioned, the system of the present application modifies the system of the 956 patent by adding a small amount of capric acid (about 1-12% as stated above) to the enhancer combination – much less than the preferred or even broader ranges taught by the 084 patent. Again I submit that these specifically claimed modifications to the 956 patent's transdermal system could not have been imparted in any way to the skilled person by the 084 patent. It is doubtless that significant trial-and-error experimentation was conducted by the inventor before these modifications were settled upon.

The Significant Improvement in Clinical Results Achieved with the System of the Present Invention Could Not Have Been Predicted by Anything in the Cited Prior Art

21. Finally, and perhaps most noteworthy, are the *in vitro* skin flux and *in vivo* clinical results obtained in the 956 patent system as compared with the system of the present

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application or its parent, which is incorporated by reference. These are summarized in the table below.

	956 Patent	Present Application or its parent
In vitro skin flux model used	Human cadaver skin on the Valia-Chien side-by-side type skin permeation cell system (Crown Glass Co., Branchburg, NJ) [Example 2 of 956 patent]	Human cadaver skin on the Valia-Chien side-by-side type skin permeation cell system (Crown Glass Co., Branchburg, NJ) [Example 2 of parent of present application]
In vitro skin flux rate for progestin	Transdermal patch containing 45% total combined enhancers, 1.10 % progestin: about **0.26 μg/cm²/hr** as calculated from Fig. 2	Transdermal patch containing 43% total combined enhancers, 1.16% progestin: about **0.16 μg/cm²/hr** as calculated from Fig. 2 of parent of present application
Clinical model	Fertile Chinese women, test period one menstrual cycle [Example 4 of 956 patent]	1. Fertile Chinese women, test period three menstrual cycles [Example 4 of parent of present application] 2. Fertile women, test period four menstrual cycles [Example 4 of present application]
Serum concentration progestin delivered from 10 cm² patch	Serum concentration ranged from about 100-280 pg/ml, but generally was 200 pg/ml or lower [Fig 4, circles]	Serum concentration ranged from about 600-2700 pg/ml but generally was in the 1000-2200 pg/ml range [Fig. 7 of parent of present application]
Serum concentration progestin delivered from two 10 cm² patches or one 20 cm² patch	Serum concentration ranged from about 250-700 pg/ml, but generally was 500 pg/ml or lower [Fig 4, squares]	Serum concentration ranged from about 900-3900 pg/ml but generally was in the 1500-3000 pg/ml range [Table 2 of present application]

22. As can be seen, the *in vitro* skin flux rate for progestin from a transdermal patch containing capric acid (data shown in parent of the present application) was actually poorer than that seen for the 956 patent's system. That is, from those data, it appears that the addition of capric acid actually decreased the effectiveness of the system for delivering progestin. Yet in the clinical studies, the steady state serum concentration of progestin delivered by a 10 or 20 cm² patch of the present invention was three- to eight-fold better than that of the 956 patent's formulation – about 1000-2200 pg/ml for a 10 cm² patch (as shown in the parent of the present application) and about 1500-3000 pg/ml for a 20 cm² patch (as shown in the present application.), versus only about 100-280 pg/ml on average for a 10 cm² patch of the 956 patent's formulation (Fig. 4 of 956 patent, see "Group A") and about 250-700 pg/ml for a 20 cm² patch of that formulation (Fig. 4 of 956 patent, see "Group B"). It is

my considered opinion that this many-fold improvement in *in vivo* progestin delivery by re-formulating the matrix to include capric acid could not have been predicted from the information presented in the 956 patent or the 084 patent. Indeed, I do not believe that these results could have been predicted from any literature.

23. In conclusion, I wish to emphasize again that transdermal drug delivery is an unpredictable and inexact science in which empirical observation and significant trial-and-error experimentation can and must play a critical role. It is for this reason, as elaborated above, that I do not believe the transdermal delivery system of the present application is in any way obvious in view of the references cited by the examiner.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issued thereon.

November 1, 2006
DATE

AGIS KYDONIEUS, PH.D.